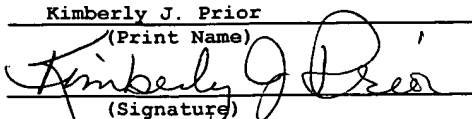


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Date: December 6, 2004

Kimberly J. Prior

(Print Name)



(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1632

Rosa Maria Rodriguez Sarmiento, et al.

Serial No.: 10/734,949

Filed: December 13, 2003

For: 3H-QUINAZOLIN-4-ONE DERIVATIVES AS MAO-B INHIBITORS

TRANSMITTAL OF CERTIFIED COPY

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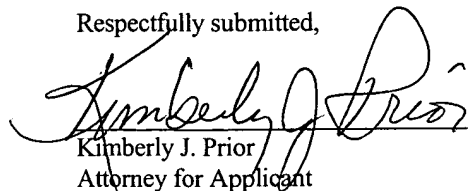
Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

<u>Country</u>	<u>Application No.</u>	<u>Filing Date</u>
Europe	02027700.0	December 13, 2002

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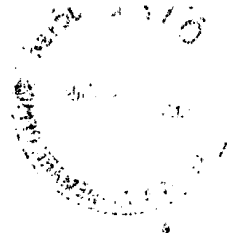
Respectfully submitted,



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Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02027700.0

**CERTIFIED COPY OF
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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Anmeldung Nr:
Application no.: 02027700.0
Demande no:

Anmeldetag:
Date of filing: 13.12.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

F. HOFFMANN-LA ROCHE AG

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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

3H-Quinazolin-4one derivatives as MAO-B inhibitors

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D239/00

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SI SK

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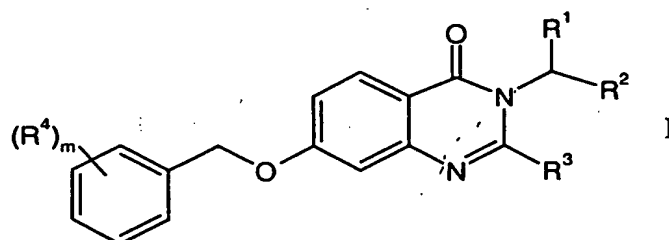
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13. Dez. 2002

Case 21247

3H-Quinazolin-4-one derivatives as MAO-B inhibitors

This invention is concerned with 3H-quinazolin-4-one derivatives of the general formula



5 wherein

R^1 is $-(CH_2)_n-CO-NR^5R^6$;
 $-(CH_2)_n-COOR^7$;
 $-(CH_2)_n-NR^5R^6$;

10 $-(CH_2)_n-CN$;
 $-(CH_2)_n-OR^8$; or
phenyl, which is unsubstituted or substituted by one to three substituents selected from halogen or fluoro(C_1-C_6)-alkyl;

R^2 is hydrogen or C_1-C_6 -alkyl;

R^3 is hydrogen, C_1-C_6 -alkyl, C_3-C_6 -cycloalkyl or benzyl;

15 R^4 is halogen, fluoro(C_1-C_6)-alkyl, cyano, C_1-C_6 -alkoxy or fluoro(C_1-C_6)-alkoxy;

R^5 and R^6 are independently from each other hydrogen or C_1-C_6 -alkyl;

R^7 is hydrogen or C_1-C_6 -alkyl;

R^8 is hydrogen or C_1 - C_6 -alkyl;

m is 1, 2 or 3; and

n is 0, 1 or 2;

as well as their pharmaceutically acceptable salts.

- 5 It has been found that the compounds of general formula I are selective monoamine oxidase B inhibitors.

Monoamine oxidase (MAO, EC 1.4.3.4) is a flavin-containing enzyme responsible for the oxidative deamination of endogenous monoamine neurotransmitters such as dopamine, serotonin, adrenaline, or noradrenaline, and trace amines, e.g. phenylethyl-
10 amine, as well as a number of amine xenobiotics. The enzyme exists in two forms, MAO-A and MAO-B, encoded by different genes (A. W. Bach et al., *Proc. Natl. Acad. Sci. USA* 1988, 85, 4934-4938) and differing in tissue distribution, structure and substrate specificity. MAO-A has higher affinity for serotonin, octopamine, adrenaline, and noradrenaline; whereas the natural substrates for MAO-B are phenylethylamine and
15 tyramine. Dopamine is thought to be oxidised by both isoforms. MAO-B is widely distributed in several organs including brain (A.M. Cesura and A. Pletscher, *Prog. Drug Research* 1992, 38, 171-297). Brain MAO-B activity appears to increase with age. This increase has been attributed to the gliosis associated with aging (C.J. Fowler et al., *J. Neural. Transm.* 1980, 49, 1-20). Additionally, MAO-B activity is significantly higher in the
20 brains of patients with Alzheimer's disease (P. Dostert et al., *Biochem. Pharmacol.* 1989, 38, 555-561) and it has been found to be highly expressed in astrocytes around senile plaques (Saura et al., *Neuroscience* 1994, 70, 755-774). In this context, since oxidative deamination of primary monoamines by MAO produces NH_3 , aldehydes and H_2O_2 , agents with established or potential toxicity, it is suggested that there is a rationale for the use of
25 selective MAO-B inhibitors for the treatment of dementia and Parkinson's disease. Inhibition of MAO-B causes a reduction in the enzymatic inactivation of dopamine and thus prolongation of the availability of the neurotransmitter in dopaminergic neurons. The degeneration processes associated with age and Alzheimer's and Parkinson's diseases may also be attributed to oxidative stress due to increased MAO activity and consequent
30 increased formation of H_2O_2 by MAO-B. Therefore, MAO-B inhibitors may act by both reducing the formation of oxygen radicals and elevating the levels of monoamines in the brain.

Given the implication of MAO-B in the neurological disorders mentioned above, there is considerable interest to obtain potent and selective inhibitors that would permit control over this enzymatic activity. The pharmacology of some known MAO-B inhibitors is for example discussed by D. Bentué-Ferrer et al. in *CNS Drugs* 1996, 6, 217-236.

5 Whereas a major limitation of irreversible and non-selective MAO inhibitor activity is the need to observe dietary precautions due to the risk of inducing a hypertensive crisis when dietary tyramine is ingested, as well as the potential for interactions with other medications (D. M. Gardner et al., *J. Clin. Psychiatry* 1996, 57, 99-104), these adverse events are of less concern with reversible and selective MAO inhibitors, in particular of MAO-B. Thus, there
10 is a need for MAO-B inhibitors with a high selectivity and without the adverse side-effects typical of irreversible MAO inhibitors with low selectivity for the enzyme.

The object of the present invention therefore is to provide compounds which must have the advantageous properties mentioned above. It has been found that compounds of
15 formula I of the present invention and their pharmaceutically acceptable salt show the potential to be highly selective MAO-B inhibitors. Subjects of the present invention are further a process for the manufacture of compounds of formula I as well as medicaments based on a compound in accordance with the invention and their manufacture as well as the use of the compounds in the control or prevention of diseases mediated by monoamine oxidase B inhibitors, and, respectively, for the production of corresponding
20 medicaments.

The following definitions of general terms used in the present patent application apply irrespective of whether the terms in question appear alone or in combination. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural forms unless the context clearly dictates otherwise.

25 The term "C₁-C₆-alkyl" ("lower alkyl") used in the present application denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, and the like.

The term "halogen" denotes fluorine, chlorine, bromine and iodine.

30 "Halogen-(C₁-C₆)-alkyl" means the lower alkyl residue as defined herein substituted in any position with one or more halogen atoms as defined herein. Examples of halogenalkyl residues include, but are not limited to, 1,2-difluoropropyl, 1,2-dichloropropyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, and 1,1,1-trifluoropropyl, and the like.

"C₁-C₆-Alkoxy" means the residue -O-R, wherein R is a lower alkyl residue as defined herein. Examples of alkoxy radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

"Pharmaceutically acceptable salts" of a compound means salts that are
5 pharmaceutically acceptable, which are generally safe, non-toxic, and neither biologically nor otherwise undesirable, and that possess the desired pharmacological activity of the parent compound. These salts are derived from an inorganic or organic acid or base. It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) of the same acid addition
10 salt.

Among compounds of the present invention certain compounds of formula I, or pharmaceutically acceptable salts thereof, are preferred.

Preferred compounds of formula I are those, wherein R³ is hydrogen.

Also preferred are compounds of formula I, wherein R³ is C₁-C₆-alkyl. Especially
15 preferred are those, wherein R³ is methyl.

Compounds of formula I, wherein R³ is C₃-C₆-cycloalkyl or benzyl, are also preferred.

Preferred compounds of formula I are further those, wherein R¹ is
-(CH₂)_n-CO-NR⁵R⁶, R⁵ and R⁶ are independently from each other hydrogen or C₁-C₆-
20 alkyl, and n is 0, 1 or 2. Especially preferred are those compounds, wherein R⁵ and R⁶ are hydrogen, and n is 0, 1 or 2.

Even more preferred are compounds of formula I, wherein R¹ is -(CH₂)_n-CO-NR⁵R⁶, R⁵ and R⁶ are hydrogen, and n is 0.

The following compounds are examples thereof:

25 2-[7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide,
2-[7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionamide,
2-[7-(4-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide,
2-[7-(4-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionamide,
2-[7-(3-fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-acetamide, and
30 2-[2-cyclopropyl-7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide.

Also preferred are compounds of formula I, wherein R^1 is $-(CH_2)_n-OR^8$, R^8 is hydrogen or C_1-C_6 -alkyl, and n is 0, 1 or 2. Especially preferred are those, wherein R^8 is methyl and n is 1.

Examples thereof are the following compounds:

- 5 7-(3-fluoro-benzyloxy)-3-(2-methoxy-ethyl)-3H-quinazolin-4-one,
7-(4-fluoro-benzyloxy)-3-(2-methoxy-ethyl)-3H-quinazolin-4-one, and
7-(3-fluoro-benzyloxy)-3-(2-methoxy-ethyl)-2-methyl-3H-quinazolin-4-one.

Further preferred are compounds of formula I, wherein R^1 is $-(CH_2)_n-NR^5R^6$, R^5 and R^6 are independently from each other hydrogen or C_1-C_6 -alkyl, and n is 0, 1 or 2.

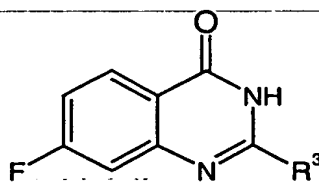
- 10 Especially preferred within this group of compounds are those, wherein R^5 and R^6 are hydrogen, and n is 0, 1 or 2.

The following compounds are examples thereof:

- 3-(2-amino-ethyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride,
3-(3-amino-propyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride,
15 3-(2-amino-ethyl)-7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one 1:1 hydrochloride, and
2-[7-(3-fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-ethyl-ammonium
chloride.

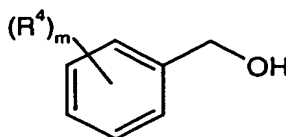
Preferred compounds of formula I are especially those, wherein R^4 is halogen or fluoro(C_1-C_6)-alkyl. More preferably, R^4 is fluoro.

- 20 The compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by reacting a compound of formula



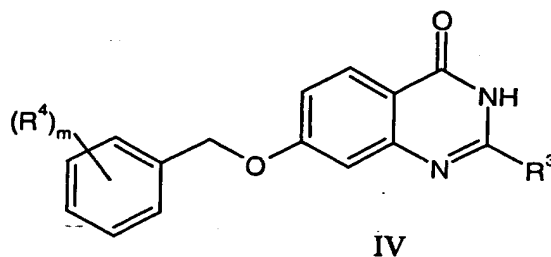
II

wherein R^3 is hydrogen, with a compound of formula

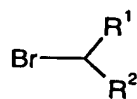


III

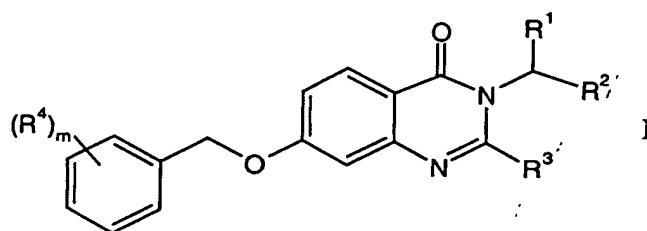
to obtain a compound of formula



wherein R^3 is hydrogen, which in turn is reacted with a compound of formula

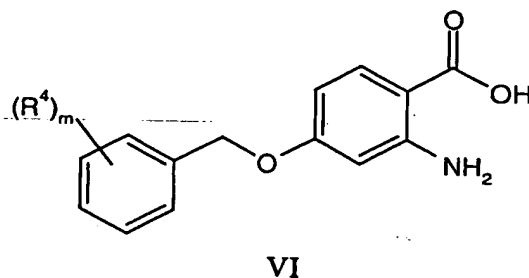


5 to obtain a compound of formula

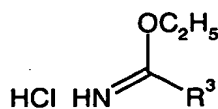


and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt, or alternatively,

reacting a compound of formula

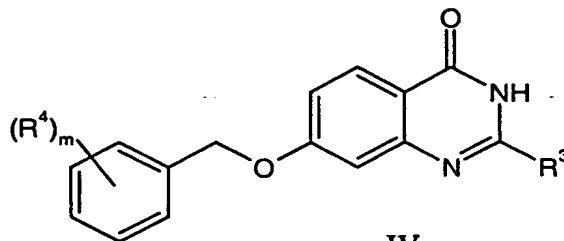


with a compound of formula



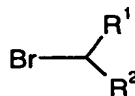
VII

to obtain a compound of formula



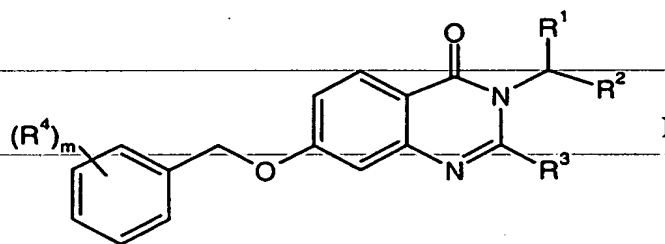
IV

5 which in turn is reacted with a compound of formula



V

to obtain a compound of formula



I

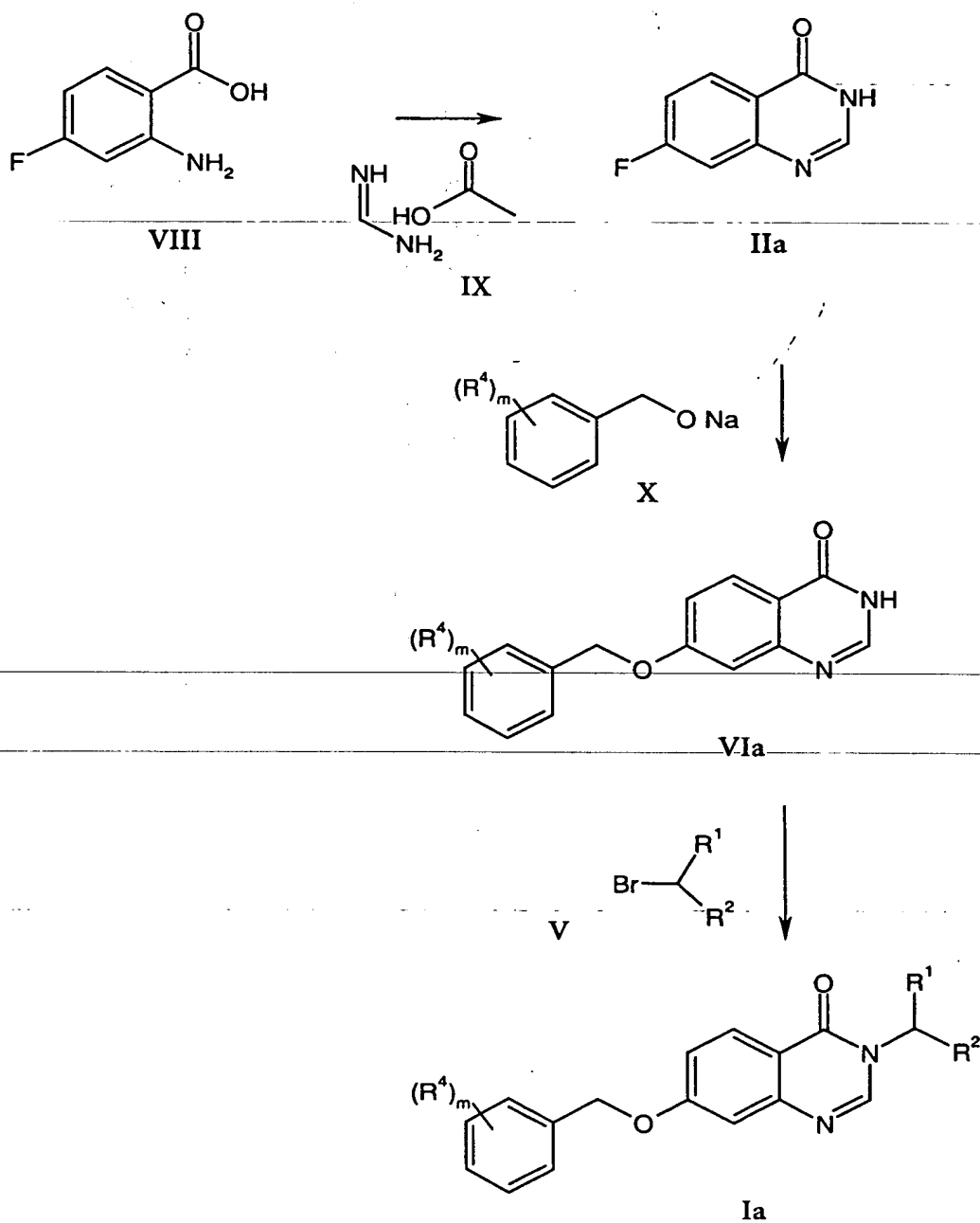
and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

10

In accordance with the present invention, compounds of general formula I can be prepared following scheme 1:

- 2-Amino-4-fluorobenzoic acid VIII is heated in the presence of formamidine acetate IX which after basification of the reaction medium affords compounds of type IIa. Subsequent reaction with the sodium salts of benzylic alcohols of type X affords compounds of type IVa which are then dissolved in 1-methyl-2-pyrrolidone (NMP) and treated with sodium hydride and an electrophile of formula V to give compounds of formula I, wherein R³ is hydrogen.

Scheme 1



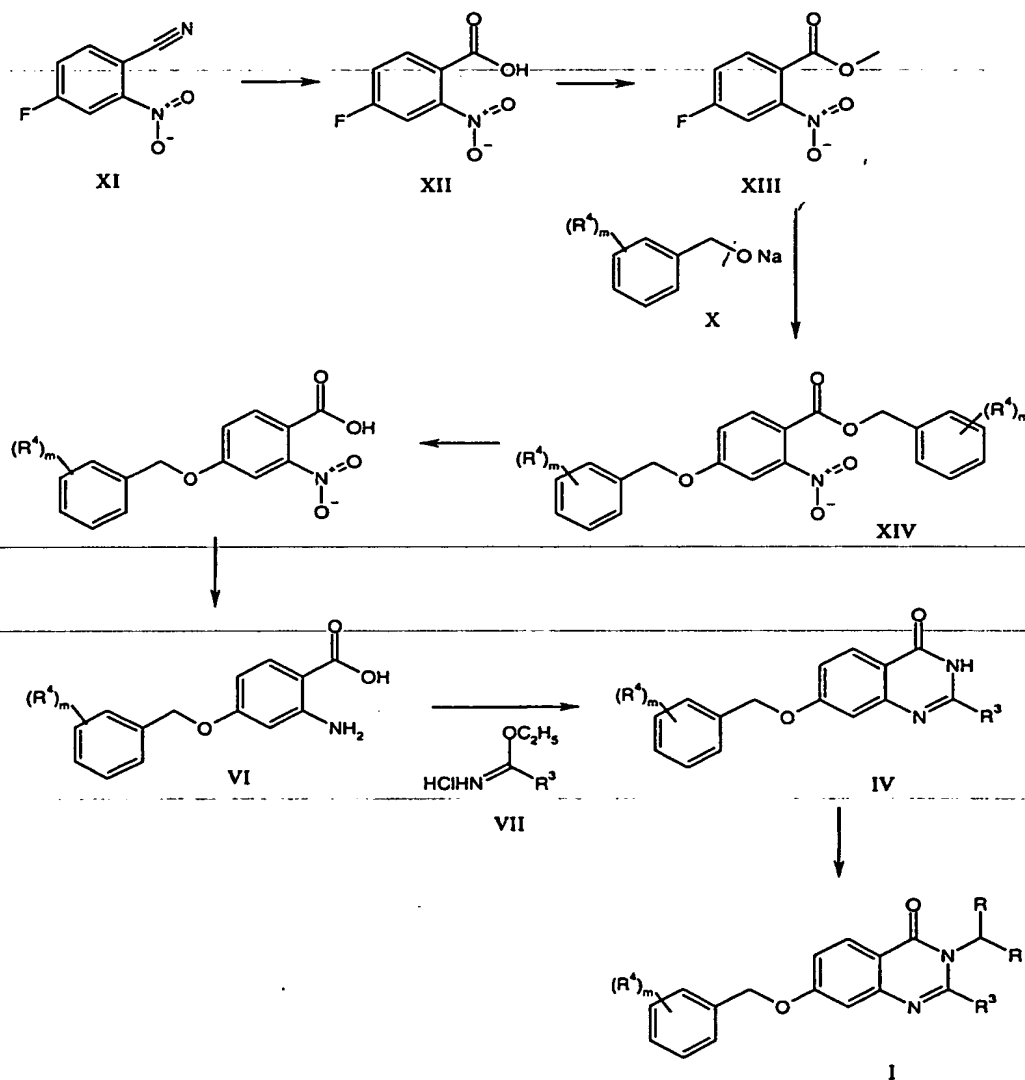
Alternatively, compounds of general formula I can be prepared according to the following scheme 2:

4-Fluoro-2-nitro-benzonitrile XI is heated in the presence of HBr and the resulting acid XII is esterified with acidic methanol to afford a compound of formula XIII.

- 5 Subsequent reaction with the sodium salts of benzylic alcohols of type X affords compounds of type XIV, which are then hydrogenated to anilines of formula VI. Treatment with acetamido hydrochloride of type VII in base (usually sodium methoxide) forms the quinazolinones IV which are then alkylated with compounds of type V to form the target compounds of formula I.

10

Scheme 2



Pharmaceutically acceptable salts of compounds of formula I can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation of pharmaceutically acceptable salts of acidic compounds.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, monoamine oxidase B inhibitors and can be used for the treatment or prevention of diseases in which MAO-B inhibitors might be beneficial. These include acute and chronic neurological disorders, cognitive disorders and memory deficits. Treatable neurological disorders are for instance traumatic or chronic degenerative processes of the nervous system, such as Alzheimer's disease, other types of dementia, minimal cognitive impairment or Parkinson's disease. Other indications include psychiatric diseases such as depression, anxiety, panic attack, social phobia, schizophrenia, eating and metabolic disorders such as obesity as well as the prevention and treatment of withdrawal syndromes induced by abuse of alcohol, nicotine and other addictive drugs. Other treatable indications may be reward deficiency syndrome (G.M. Sullivan, International patent application No. WO 01/34172 A2), peripheral neuropathy caused by cancer chemotherapy (G. Bobotas, International Patent Application No. WO 97/33572 A1), or the treatment of multiple sclerosis (R.Y. Harris, International patent application No. WO 96/40095 A1) and other neuroinflammatory diseases.

The pharmacological activity of the compounds was tested using the following method:

The cDNA's encoding human MAO-A and MAO-B were transiently transfected into EBNA cells using the procedure described by E.-J. Schlaeger and K. Christensen (Transient Gene Expression in Mammalian Cells Grown in Serum-free Suspension Culture; Cytotechnology, 15: 1-13, 1998). After transfection, cells were homogenised by means of a Polytron homogeniser in 20 mM Tris HCl buffer, pH 8.0, containing 0.5 mM EGTA and 0.5 mM phenylmethanesulfonyl fluoride. Cell membranes were obtained by centrifugation at 45,000 x g and, after two rinsing step with 20 mM Tris HCl buffer, pH 8.0, containing 0.5 mM EGTA, membranes were eventually re-suspended in the above buffer and aliquots stored at -80 °C until use.

MAO-A and MAO-B-enzymatic activity was assayed in 96-well-plates using a spectrophotometric assay adapted from the method described by M. Zhou and N. Panchuk-Voloshina (A One-Step Fluorometric Method for the Continuous Measurement of Monoamine Oxidase Activity, Analytical Biochemistry, 253: 169-174, 1997). Briefly,
5 membrane aliquots were incubated in 0.1 M potassium phosphate buffer, pH 7.4, for 30 min at 37°C with or without various concentrations of the compounds. After this period, the enzymatic reaction was started by the addition of the MAO substrate tyramine together with 1 U/ml horse-radish peroxidase (Roche Biochemicals) and 80 µM N-acetyl-3,7,-dihydroxyphenoxazine (Amplex Red, Molecular Probes). The samples were further
10 incubated for 30 min at 37 °C in a final volume of 200 µl and absorbance was then determined at a wavelength of 570 nm using a SpectraMax plate reader (Molecular Devices). Background (non-specific) absorbance was determined in the presence of 10 µM clorgyline for MAO-A or 10 µM L-deprenyl for MAO-B.

IC₅₀ values were determined from inhibition curves obtained using nine inhibitor
15 concentrations in duplicate, by fitting data to a four parameter logistic equation using a computer program.

The compounds of the present invention are specific MAO-B inhibitors. The activities of compounds of formula I as measured in the assay described above are in the range of 10 µM or less, typically of 1 µM or less, and ideally 0.3 µM or less.

20 The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g.
25 in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets,
30 dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as
35 alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary.

Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They may also contain other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I or pharmaceutically acceptable salts thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Example 1

2-[7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

25 a) 7-Fluoro-3H-quinazolin-4-one

A mixture of 2-amino-4-fluorobenzoic acid (14.6 g, 94 mmol) and formamidine acetate (19.6 g, 18.8 mmol) in 2-methoxyethanol (110 mL) was heated at 130 °C for 18 h. After cooling, the mixture was half evaporated and an off-white solid formed. The mixture was diluted with ammonia (25%, 10 mL in 90 mL water) and the solid filtered off and washed with water. The solid was then washed with hexane and dried under high vacuum to afford the title compound (12.5 g, 81%) as an off-white solid. MS: m/e = 165.2 (M+H⁺).

b) 7-(3-Fluoro-benzyloxy)-3H-quinazolin-4-one

Sodium (1.8 g, 78.6 mmol) was added portionwise to 3-fluorobenzyl alcohol and the resulting mixture heated at 80-90 °C for 4 h under Argon. The resulting suspension was cooled to room temperature and 7-fluoro-3H-quinazolin-4-one (3.2 g, 19.5 mmol) was added and the resulting mixture heated at 130-140 °C for 14 h. The solid formed was then dissolved with water (400 mL) and the mixture acidified to pH 3-4 with HCl (4 N). The resulting precipitate was then filtered off, washed with water (100 mL) and diethylether (100 mL). Recrystallisation from tetrahydrofuran : ethylacetate (1:1) afforded the title compound (3.2 g, 61%) as white crystals. MS: $m/e = 271.3$ ($M+H^+$).

10 c) 2-[7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

A mixture of 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) and sodium hydride (55%, 36 mg, 0.81 mmol) in N-methylpyrrolidinone (5 mL) was heated at 60 °C for 1 h. Then bromacetamide (117 mg, 0.85 mmol) was added and the resulting mixture was heated at 80 °C for 1 h. After cooling to room temperature, water (50 mL) was added and the resulting precipitate was washed with methanol and diethylether and then dried under high vacuum to afford the title compound (200 mg, 83%) as an off-white solid. MS: $m/e = 328.3$ ($M+H^+$).

Example 2

2-[7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionamide

20 As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (190 mg, 75%) (using 2-bromopropionamide instead of bromacetamide) which was obtained as a white solid. MS: $m/e = 342.3$ ($M+H^+$).

Example 3

7-(3-Fluoro-benzyloxy)-3-(2-methoxy-ethyl)-3H-quinazolin-4-one

25 As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (165 mg, 68%) [using (2-bromomethyl)-methylether instead of bromacetamide] which was obtained as a white solid after crystallisation from diethylether : heptane. MS: $m/e = 342.3$ ($M+H^+$).

Example 4

3-(2-Amino-ethyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride

a) 2-[7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-ethyl}-carbamic acid tert-butyl ester

- 5 As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (175 mg, 57%) [using 2-(Boc-amino)-ethylbromide instead of bromacetamide] which was obtained as a white solid after crystallisation from diethylether : heptane. MS: $m/e = 342.3$ ($M+H^+$).

b) 3-(2-Amino-ethyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride

- 10 A mixture of {2-[7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-ethyl}-carbamic acid tert-butyl ester (150 mg, 0.36 mmol) and HCl in dioxane (4 N, 3 mL) was stirred at room temperature for 72 h. The precipitate was filtered off and washed with diethylether to afford the title compound (120 mg, 86%) as a white solid. MS: $m/e = 314.3$ ($M+H^+$).

Example 5

15 [7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetic acid ethyl ester

As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (170 mg, 65%) [using ethyl bromoacetate instead of bromacetamide] which was obtained as a white solid. MS: $m/e = 357.3$ ($M+H^+$).

Example 6

20 Fluoro-[7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetic acid ethyl ester

- As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (100 mg, 36%) [using ethyl bromfluoroacetate instead of bromacetamide] which was obtained as a white solid after purification by chromatography (SiO_2 , CH_2Cl_2 : 2N NH_3 /MeOH 99:1 to 9:1) and crystallisation from
25 diethylether : heptane. MS: $m/e = 375.4$ ($M+H^+$).

Example 7

2-[7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionic acid ethyl ester

As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (240 mg, 88%) [using ethyl 2-bromo

propionate instead of bromacetamide] which was obtained as a colourless oil after purification by chromatography (SiO_2 , CH_2Cl_2 : 2N NH_3 /MeOH 99:1 to 9:1). MS: $m/e = 371.3$ ($\text{M}+\text{H}^+$).

Example 8

5 [7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetic acid tert-butyl ester

As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (277 mg, 97%) [using tert-butyl-bromacetate instead of bromacetamide] which was obtained as a white solid after purification by chromatography (SiO_2 , CH_2Cl_2 : 2N NH_3 /MeOH 99:1 to 9:1). MS: $m/e = 385.3$ ($\text{M}+\text{H}^+$).

10

Example 9

2-[7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionic acid tert-butyl ester

As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (245 mg, 83%) [using 2-bromopropionic acid tert-butyl ester instead of bromacetamide] which was obtained as a white solid after
15 purification by chromatography (SiO_2 , CH_2Cl_2 : 2N NH_3 /MeOH 99:1 to 9:1). MS: $m/e = 385.3$ ($\text{M}+\text{H}^+$).

Example 10

3-(3-Amino-propyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride

20 a) {3-[7-(3-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propyl}-carbamic acid tert-butyl ester

As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (312 mg, 99%) [using 3-(Boc-amino)propyl-bromide instead of bromacetamide] which was obtained as a white solid after purification by chromatography (SiO_2 , CH_2Cl_2 : 2N NH_3 /MeOH 99:1 to 9:1). MS: $m/e = 428.5$ ($\text{M}+\text{H}^+$).

25 b) 3-(3-Amino-propyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride

A mixture of {3-[7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propyl}-carbamic acid tert-butyl ester (275 mg, 0.64 mmol) and HCl in dioxane (4 N, 8 mL) was stirred at rt for 16 h. The precipitate was filtered off and recrystallised from EtOH : ether to afford the title compound (120 mg, 47%) as a white solid. MS: $m/e = 328.3$ ($\text{M}+\text{H}^+$).

Example 11

3-(3-Fluoro-benzyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one

As described for example 1c, 7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (200 mg, 0.74 mmol) was converted to the title compound (253 mg, 90%) [using 3-fluorobenzyl bromide instead of bromacetamide] which was obtained as a white solid after purification by chromatography (SiO₂, CH₂Cl₂: 2N NH₃/MeOH 99:1 to 9:1). MS: m/e = 379.3 (M+H⁺).

Example 12

2-[7-(4-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

a) 7-(4-Fluoro-benzyloxy)-3H-quinazolin-4-one

10 A mixture of sodium hydride (55%, 3.2 g, 73 mmol), 4-fluorobenzyl alcohol (9.2 g, 73 mmol) and 7-fluoro-3H-quinazolin-4-one (3.0 g, 18 mmol) in DMF (75 mL) was heated at 140 °C for 2 h. The resulting suspension was cooled to room temperature and the mixture acidified to pH 3 with HCl (conc.). The resulting precipitate was then filtered off, washed with water and diethylether. Partial purification by chromatography on silica gel
15 eluting with ethyl acetate : hexane (2:1) afforded the title compound (3.2 g, 66%) as an off-white solid. MS: m/e = 271.3 (M+H⁺).

b) 2-[7-(4-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

As described for example 1c, 7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one (Example 12a, 200 mg, 0.74 mmol) was converted to the title compound (20 mg, 8%) which was
20 obtained as a white solid after purification by HPLC (Waters Xterra RP18 (5 µm x 50 x19mm) eluting with AcCN/ 0.1%TFA/Water. MS: m/e = 328.3 (M+H⁺).

Example 13

2-[7-(4-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionamide

As described for example 1c, 7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one (400 mg, 1.5 mmol) was converted to the title compound (37 mg, 7%) (using 2-bromopropionamide instead of bromacetamide) which was obtained as a white solid after purification by HPLC
25 (Waters Xterra RP18 (5 µm x 50 x19mm) eluting with AcCN/ 0.1%TFA/Water. MS: m/e = 340.2 (M+H⁺).

Example 14

7-(4-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetic acid ethyl ester

As described for example 1c, 7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one (400 mg, 1.5 mmol) was converted to the title compound (83 mg, 16%) (using ethyl bromoacetate instead of bromacetamide) which was obtained as a white solid after purification by HPLC (Waters Xterra RP18 (5 μ m x 50 x19mm) eluting with AcCN/ 0.1%TFA/Water. MS: m/e = 357.3 (M+H⁺).

Example 15

2-[7-(4-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionic acid ethyl ester

As described for example 1c, 7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one (400 mg, 1.5 mmol) was converted to the title compound (32 mg, 6%) (using ethyl-2-bromopropionate instead of bromacetamide) which was obtained as a white solid after purification by HPLC (Waters Xterra RP18 (5 μ m x 50 x19mm) eluting with AcCN/ 0.1%TFA/Water. MS: m/e = 371.3 (M+H⁺).

Example 16

7-(4-Fluoro-benzyloxy)-3-(2-methoxy-ethyl)-3H-quinazolin-4-one

As described for example 3, 7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one (400 mg, 1.5 mmol) was converted to the title compound (115 mg, 24%) which was obtained as a white solid after purification by HPLC (Waters Xterra RP18 (5 μ m x 50 x19mm) eluting with AcCN/ 0.1%TFA/Water. MS: m/e = 329.1 (M+H⁺).

Example 17

3-(2-Amino-ethyl)-7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one 1:1 hydrochloride

a) [2-[7-(4-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-ethyl]-carbamic acid tert-butyl ester

As described for example 10a, 7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one (300 mg, 1.1 mmol) was converted to the title compound (105 mg, 23%) which was obtained as a white solid after purification by HPLC (Waters Xterra RP18 (5 μ m x 50 x19mm) eluting with AcCN/ 0.1%TFA/Water. MS: m/e = 414.5 (M+H⁺).

b) 3-(2-Amino-ethyl)-7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one 1:1 hydrochloride

As described for example 10b, {2-[7-(4-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-ethyl}-carbamic acid tert-butyl ester (102 mg, 0.25 mmol) was converted to the title compound (84 mg, 97%) which was obtained as a white solid. MS: m/e = 314.2 (M+H⁺).

Example 18

5 3-[7-(4-Fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionamide

As described for example 1c, 7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one (300 mg, 1.1 mmol) was converted to the title compound (72 mg, 19%) (using 3-bromopropionamide instead of bromacetamide) which was obtained as a white solid after purification by HPLC (Waters Xterra RP18 (5 µm x 50 x 19mm) eluting with AcCN/ 0.1% TFA/Water. MS: m/e =
10 342.1 (M+H⁺).

Example 19

2-[7-(3-Fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-acetamide

a) 4-Fluoro-2-nitro-benzoic acid

A mixture of 4-fluoro-2-nitro-benzonitrile (12.2 g, 73.7 mmol) suspended in HBr (48%,
15 74.5 mL, 664 mmol) was heated at 130 °C for 6.5 h. After cooling to room temperature water (1 L) was added and the resulting precipitate was washed with water and hexane to afford the title compound (11.0 g, 81%) as a light brown solid. MS: m/e = 183.9 (M-H).

b) 4-Fluoro-2-nitro-benzoic acid methyl ester

A mixture of 4-fluoro-2-nitro-benzoic acid (10.9 g, 58.8 mmol) in methanol (120 mL)
20 containing sulfuric acid (1.8 g, 18.7 mmol) was heated under reflux for 41 h. After cooling to room temperature the mixture was poured into sodium hydrogen carbonate (sat. 250 mL), and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine (100 mL) dried and evaporated to leave the title compound (10.7 g, 91%) as a light brown liquid. MS: m/e = 199.0 (M-H).

25 c) 4-(3-Fluoro-benzyloxy)-2-nitro-benzoic acid (3-fluoro-benzyl) ester and 4-(3-fluoro-benzyloxy)-2-nitro-benzoic acid methyl ester

A mixture of 4-fluoro-2-nitro-benzoic acid methyl ester (9.2 g, 46.3 mmol), 3-fluorobenzyl alcohol (16.7 g, 132.4 mmol) and potassium carbonate (12.8 g, 92.6 mmol) in DMF (210 mL) was heated at 65 °C for 48 h. After cooling to room temperature, the
30 mixture was poured into water (400 mL), and extracted with diethyl ether (3 x 100 mL). The combined extracts were washed with brine (100 mL) dried and evaporated.

Purification by chromatography on silica gel eluting with ethyl acetate : hexane (1:1) afforded the title compound (14.0 g, 76%) as a light yellow liquid.

d) 4-(3-Fluoro-benzyloxy)-2-nitro-benzoic acid

5 A mixture of 4-(3-fluoro-benzyloxy)-2-nitro-benzoic acid (3-fluoro-benzyl) ester and 4-(3-fluoro-benzyloxy)-2-nitro-benzoic acid methyl ester (14.0 g, 35.0 mmol) in THF (120 mL) and water (120 mL), containing lithium hydroxide monohydrate (2.94 g, 70.1 mmol) was stirred at room temperature for 48 h. Then the mixture was poured into sodium hydroxide (2 N, 50 mL) and then the mixture extracted with diethyl ether (3 x 150 mL). The aqueous phase was then adjusted to pH 2 with HCl. Then the mixture was poured into 10 sodium hydroxide (2 N, 50 mL) and the aqueous phase was then adjusted to pH 5.2 with HCl then the mixture extracted with diethyl ether (3 x 100 mL). The combined extracts were then washed with brine (100 mL) dried and evaporated to afford title compound (6.6 g, 65%) as a light yellow solid. MS: m/e = 290.0 (M-H).

e) 2-Amino-4-(3-fluoro-benzyloxy)-benzoic acid

15 A mixture of 4-(3-fluoro-benzyloxy)-2-nitro-benzoic acid (7.2 g, 24.8 mmol) in ethyl acetate (150 mL) in the presence of Pt/C (5%, 1.0 g) was hydrogenated at room temperature and pressure for 3.5 h. The mixture was then filtered and the filtrate was evaporated. The resulting light brown solid was triturated with dichloromethane (DCM) to afford the title compound (5.2 g, 80%) as an off-white solid. MS: m/e = 260.1 (M-H).

20 Alternatively, a mixture of 4-(3-fluoro-benzyloxy)-2-nitro-benzoic acid (6.6 g, 22.8 mmol) in ethyl acetate (140 mL) in the presence of Pd/C (5%, 1.0 g) was hydrogenated at room temperature and pressure for 3.5 h. The mixture was then filtered and the filtrate was evaporated. The resulting light brown solid was triturated with DCM to afford the title compound (5.1 g, 87%) as an off-white solid.

25 f) 7-(3-Fluoro-benzyloxy)-2-methyl-3H-quinazolin-4-one

To a mixture of 2-amino-4-(3-fluoro-benzyloxy)-benzoic acid (2.0 g, 7.7 mmol) and ethyl acetamidate HCl (1.9 g, 15.3 mmol) in methanol (30 mL) was added sodium methoxide (5.4 M, 0.83 g, 15.3 mmol) and the resulting mixture was heated under reflux for 19 h. After this time ethyl acetamidate HCl (1.9 g, 15.3 mmol) and sodium methoxide (5.4 M, 30 0.83 g, 15.3 mmol) was added and the resulting mixture heated for another 1 h. After cooling to room temperature the mixture was poured into water (40 mL) and then the resulting precipitate was stirred for 2 h, and then filtered off to afford the title compound (2.1 g, 97%) as an off-white solid. MS: m/e = 283.1 (M-H).

g) 2-[7-(3-Fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-acetamide

As described for example 1c, 7-(3-fluoro-benzyloxy)-2-methyl-3H-quinazolin-4-one (250 mg, 0.88 mmol) was converted to the title compound (218 mg, 73%) which was obtained as a white solid after trituration with dichloromethane (DCM). MS: $m/e = 342.1$ ($M+H^+$).

5

Example 20

7-(3-Fluoro-benzyloxy)-3-(2-methoxy-ethyl)-2-methyl-3H-quinazolin-4-one

As described for example 3, 7-(3-fluoro-benzyloxy)-2-methyl-3H-quinazolin-4-one (250 mg, 0.88 mmol) was converted to the title compound (150 mg, 45%) which was obtained as a white solid after purification by chromatography (SiO_2 , EtOAc:heptane 1:3 to 2:1).

10 MS: $m/e = 343.1$ ($M+H^+$).

Example 21

2-[7-(3-Fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-ethyl-ammonium chloride

15 a) {2-[7-(3-Fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-ethyl}-carbamic acid tert-butyl ester

As described for example 4a, 7-(3-fluoro-benzyloxy)-2-methyl-3H-quinazolin-4-one (250 mg, 0.88 mmol) was converted to the title compound (72 mg, 18%) which was obtained as a white solid after purification by chromatography (SiO_2 , EtOAc:heptane 1:4 to 2:1). MS: $m/e = 428.3$ ($M+H^+$).

20 b) 2-[7-(3-Fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-ethyl-ammonium chloride

As described for example 4b, {2-[7-(3-fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-ethyl}-carbamic acid tert-butyl ester (50 mg, 0.12 mmol) was converted to the title compound (45 mg, 85%) which was obtained as a white solid after purification by
25 chromatography (SiO_2 , EtOAc:heptane 1:4 to 2:1). MS: $m/e = 328.2$ ($M+H^+$).

Example 22

2-[7-(3-Fluoro-benzyloxy)-2-isopropyl-4-oxo-4H-quinazolin-3-yl]-acetamide

a) 7-(3-Fluoro-benzyloxy)-2-isopropyl-3H-quinazolin-4-one

As described for example 19f, 2-amino-4-(3-fluoro-benzyloxy)-benzoic acid (1 g, 3.8 mmol) was converted to the title compound (196 mg, 16%) [using ethyl isopropylamide HCl instead of ethyl acetamide HCl] which was obtained as a white solid after purification by chromatography (SiO₂, dichloromethane:MeOH 95:5 to 85:15). MS: m/e = 330.1 (M+NH₄⁺).

b) 2-[7-(3-Fluoro-benzyloxy)-2-isopropyl-4-oxo-4H-quinazolin-3-yl]-acetamide

As described for example 1c, 7-(3-fluoro-benzyloxy)-2-isopropyl-3H-quinazolin-4-one (80 mg, 0.26 mmol) was converted to the title compound (84 mg, 89%) which was obtained as a white solid after trituration with dichloromethane. MS: m/e = 370.2 (M+H⁺).

Example 23

15 [7-(3-Fluoro-benzyloxy)-2-isopropyl-4-oxo-4H-quinazolin-3-yl]-acetonitrile

To a mixture of 2-[7-(3-fluoro-benzyloxy)-2-isopropyl-4-oxo-4H-quinazolin-3-yl]-acetamide (50 mg, 0.14 mmol) in dimethylformamide (0.5 mL), dichloromethane (2 mL) was added N-ethyl-N,N-diisopropylamine (26.2 mg, 0.2 mmol) and the resulting mixture cooled to -78 °C. Then trifluorosulfonic anhydride (49.6 mg, 0.18 mmol) was added and the reaction mixture allowed to warm up to room temperature over 30 min. The resulting mixture was then poured onto sodium hydrogen carbonate (sat. 5 mL), and the mixture extracted with diethylether (3 x 5 mL). The combined extracts were then washed with brine, dried and evaporated to leave a light yellow solid. Purification by chromatography (SiO₂, EtOAc:heptane 1:1 to 85:15) afforded the title compound (26 mg, 55%) as a white solid. MS: m/e = 352.2 (M+H⁺).

Example 24

2-[2-Cyclopropyl-7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

a) 2-Cyclopropyl-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one

As described for example 19f, 2-amino-4-(3-fluoro-benzyloxy)-benzoic acid (1.0 g, 3.8 mmol) was converted to the title compound (607 mg, 49%) [using ethyl cyclopropyl-amidate HCl instead of ethyl acetamidate HCl] which was obtained as a white solid after trituration with diethylether. MS: $m/e = 311.2$ ($M+H^+$).

b) 2-[2-Cyclopropyl-7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

As described for example 1c, 2-cyclopropyl-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (80 mg, 0.26 mmol) was converted to the title compound (98 mg, 65%) which was obtained as a white solid after purification by chromatography (SiO_2 , dichloromethane:MeOH 98:2 to 9:1). MS: $m/e = 368.1$ ($M+H^+$).

Example 25

2-Cyclopropyl-7-(3-fluoro-benzyloxy)-3-(2-methoxy-ethyl)-3H-quinazolin-4-one

As described for example 3, 2-cyclopropyl-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (150 mg, 0.48 mmol) was converted to the title compound (15 mg, 8%) which was obtained as a white solid after purification by chromatography (SiO_2 , dichloromethane : MeOH 95:5). MS: $m/e = 369.2$ ($M+H^+$).

Example 26

[2-Cyclopropyl-7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetic acid methyl ester

As described for example 1c, 2-cyclopropyl-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (100 mg, 0.3 mmol) was converted to the title compound (33 mg, 27%) [using methyl bromoacetate instead of bromacetamide] which was obtained as a white solid after purification by chromatography (SiO_2 , EtOAc:heptane 1:9 to 1:1). MS: $m/e = 383.3$ ($M+H^+$).

Example 27

2-[2-Benzyl-7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

a) 2-Benzyl-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one

As described for example 19f, 2-amino-4-(3-fluoro-benzyloxy)-benzoic acid (1.0 g, 3.8 mmol) was converted to the title compound (731 mg, 53%) [using ethyl benzylamidate HCl instead of ethyl acetamidate HCl] which was obtained as a white solid after trituration with diethylether. MS: $m/e = 361.2$ ($M+H^+$).

b) 2-[2-Benzyl-7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide

As described for example 1c, 2-benzyl-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one (150 mg, 0.42 mmol) was converted to the title compound (94 mg, 54%) which was obtained as a white solid after purification by chromatography (SiO_2 , dichlormethane : MeOH 99:1 to 9:1). MS: $m/e = 418.2$ ($M+H^+$).

Example A

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
Active ingredient	100
5 Powdered lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
10 Tablet weight	<u>250</u>

Example B

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
Active ingredient	200
15 Powdered lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
20 Tablet weight	<u>400</u>

Example C

Capsules of the following composition are produced:

	<u>mg/Capsule</u>
Active ingredient	50
5 Crystalline lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	<u>150</u>

- 10 The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

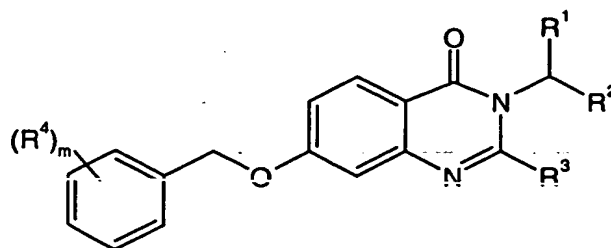
Example D

- 15 An injection solution may have the following composition and is manufactured in usual manner:

	Active substance	1.0 mg
	1 N HCl	20.0 μ l
	acetic acid	0.5 mg
20	NaCl	8.0 mg
	phenol	10.0 mg
	1 N NaOH	q.s. ad pH 5
	H ₂ O	q.s. ad 1 ml

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1. Compounds of the general formula



I

wherein

- 5 R^1 is $-(CH_2)_n-CO-NR^5R^6$;
 $-(CH_2)_n-COOR^7$;
 $-(CH_2)_n-NR^5R^6$;
 $-(CH_2)_n-CN$;
 $-(CH_2)_n-OR^8$; or
 10 phenyl, which is unsubstituted or substituted by one to three substituents selected from halogen or fluoro(C_1-C_6)-alkyl;

 R^2 is hydrogen or C_1-C_6 -alkyl;

 R^3 is hydrogen, C_1-C_6 -alkyl, C_3-C_6 -cycloalkyl or benzyl;

 R^4 is halogen, fluoro(C_1-C_6)-alkyl, cyano, C_1-C_6 -alkoxy or fluoro(C_1-C_6)-alkoxy;
 15 R^5 and R^6 are independently from each other hydrogen or C_1-C_6 -alkyl;

 R^7 is hydrogen or C_1-C_6 -alkyl;

 R^8 is hydrogen or C_1-C_6 -alkyl;

 m is 1, 2 or 3; and

 n is 0, 1 or 2;
 20 as well as their pharmaceutically acceptable salts.

2. Compounds of formula I according to claim 1, wherein R^3 is hydrogen.

3. Compounds of formula I according to claim 1, wherein R^3 is C_1-C_6 -alkyl.

4. Compounds according to claim 3, wherein R^3 is methyl.

5. Compounds according to claim 1, wherein R^3 is C_3 - C_6 -cycloalkyl or benzyl.
6. Compounds according to any one of claims 1 to 5, wherein R^1 is $-(CH_2)_n-CO-NR^5R^6$, R^5 and R^6 are independently from each other hydrogen or C_1 - C_6 -alkyl, and n is 0, 1 or 2.
- 5 7. Compounds according to claim 6, wherein R^5 and R^6 are hydrogen, and n is 0, 1 or 2.
8. Compounds according to claim 7, wherein n is 0.
9. Compounds according to claim 8, which compounds are selected from the group consisting of
- 10 2-[7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide,
2-[7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionamide,
2-[7-(4-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide,
2-[7-(4-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-propionamide,
2-[7-(3-fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-acetamide, and
15 2-[2-cyclopropyl-7-(3-fluoro-benzyloxy)-4-oxo-4H-quinazolin-3-yl]-acetamide.
10. Compounds according to any one of claims 1 to 5, wherein R^1 is $-(CH_2)_n-OR^8$, R^8 is hydrogen or C_1 - C_6 -alkyl, and n is 0, 1 or 2.
11. Compounds according to claim 10, wherein R^8 is methyl and n is 1.
12. Compounds according to claim 11, which compounds are selected from the
- 20 group consisting of
7-(3-fluoro-benzyloxy)-3-(2-methoxy-ethyl)-3H-quinazolin-4-one,
7-(4-fluoro-benzyloxy)-3-(2-methoxy-ethyl)-3H-quinazolin-4-one, and
7-(3-fluoro-benzyloxy)-3-(2-methoxy-ethyl)-2-methyl-3H-quinazolin-4-one.
13. Compounds according to any one of claims 1 to 5, wherein R^1 is
- 25 $-(CH_2)_n-NR^5R^6$, R^5 and R^6 are independently from each other hydrogen or C_1 - C_6 -alkyl, and n is 0, 1 or 2.
14. Compounds according to claim 13, wherein R^5 and R^6 are hydrogen, and n is 0, 1 or 2.
15. Compounds according to claim 14, which compounds are selected from the
- 30 group consisting of
3-(2-amino-ethyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride,
3-(3-amino-propyl)-7-(3-fluoro-benzyloxy)-3H-quinazolin-4-one 1:2 hydrochloride,

3-(2-amino-ethyl)-7-(4-fluoro-benzyloxy)-3H-quinazolin-4-one 1:1 hydrochloride, and
2-[7-(3-fluoro-benzyloxy)-2-methyl-4-oxo-4H-quinazolin-3-yl]-ethyl-ammonium
chloride.

16. Compounds according to any one of claims 1 to 15, wherein R^4 is halogen or
5 fluoro(C_1 - C_6)-alkyl.

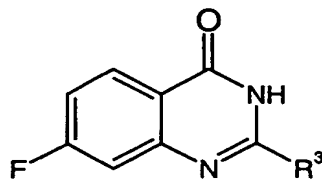
17. Compounds according to claim 16, wherein R^4 is fluoro.

18. A medicament containing one or more compounds as claimed in any one of
claims 1 to 17 and pharmaceutically acceptable excipients for the treatment and
prevention of diseases which are mediated by monoamine oxidase B inhibitors.

10 19. The medicament according to claim 18 for the treatment and prevention of
Alzheimer's disease and senile dementia.

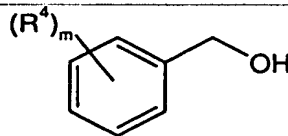
20. A process for the manufacture of compounds of formula I according to any one
of claims 1 to 17 as well as their pharmaceutically acceptable salts, which process comprises

a) reacting a compound of formula

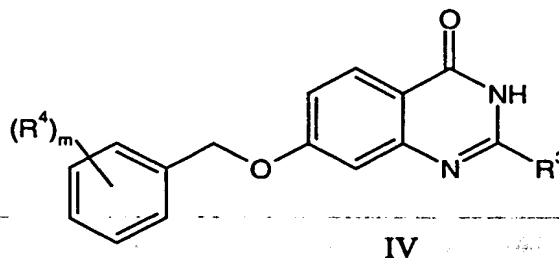


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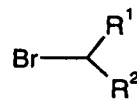
wherein R^3 is hydrogen, with a compound of formula



to obtain a compound of formula

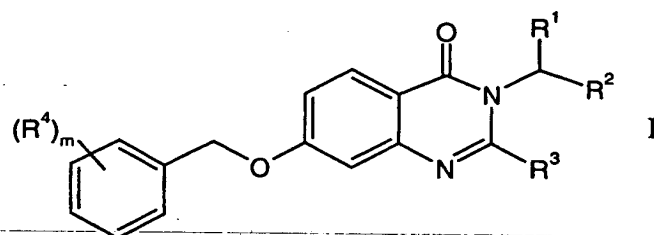


wherein R^3 is hydrogen, which in turn is reacted with a compound of formula



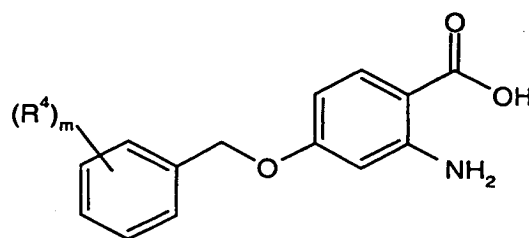
V

to obtain a compound of formula



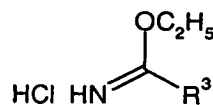
- 5 and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt, or

b) reacting a compound of formula



VI

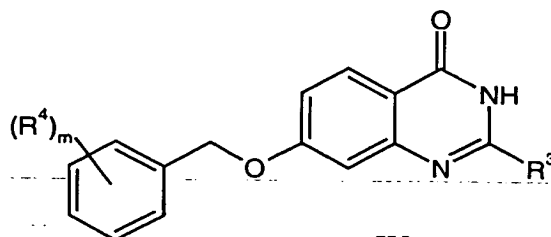
with a compound of formula



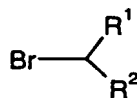
VII

10

to obtain a compound of formula

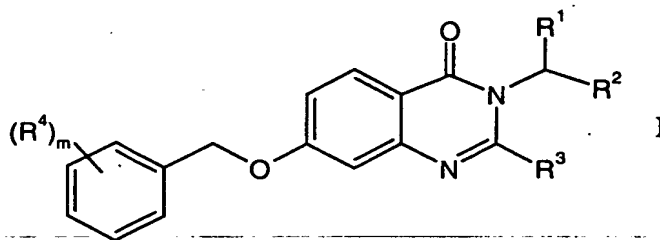


which in turn is reacted with a compound of formula



V

to obtain a compound of formula



I

- 5 and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

21. A compound of formula I according to any one of claims 1 to 17, when manufactured by a process according to claim 20.

22. A compound of formula I according to any one of claims 1 to 17 as well as its
10 pharmaceutically acceptable salts for the treatment or prevention of diseases.

23. The use of a compound of formula I according to any one of claims 1 to 17 as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

- 15 24. The use according to claim 23, wherein the disease is Alzheimer's disease or senile dementia.

25. The invention as herein before described.

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